

**REMARKS**

This amendment is being filed concurrently with a Request for Continued Examination in this application.

Applicants have amended claim 24 to recite:

24. (Currently Amended) A method of introducing a nucleic acid encoding desired molecule into for stable and efficient transformation of cardiomyocytes which comprises: infusing a recombinant adeno-associated virus (AAV) vector into a coronary artery or a coronary sinus of an animal in an amount of about  $1 \times 10^5$  to about  $1 \times 10^9$  infectious units (IU) AAV per gram body weight and for a time sufficient to stably and efficiently transduce cardiomyocytes perfused through said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid molecule operably linked to a control region, said nucleic acid molecule encoding said desired molecule an angiogenic protein.

Applicants have cancelled claims 41, 42, 44, 46 and 47 without prejudice and expressly reserve the right to pursue the subject matter of the cancelled claims in one or more subsequent applications.

An Advisory Action issued in this application on October 28, 2004 entering applicants' September 10, 2004 Amendment and Response. A notice of Appeal was filed September 21, 2004 and as such this application is still pending.

In the Advisory Action, the Examiner contends that all the claims stand rejected under one of more of 35 U.S.C. 102, 103 or 112, first paragraph for purportedly being anticipated or rendered obvious by international patent application number WO 98/50079 ("Hammond"), or for being purportedly non-enabled. Applicants respectfully disagree and in view of the foregoing amendments to the claims and the following remarks request that the Examiner reconsider and withdraw the rejections of the claims and pass the application to issue.

Prior to applicants' invention Kaplitt et al. (1996) Am Thorac. Surg 62:1669-1676 ("Kaplitt") reported that rAAV could transduce cardiomyocytes *in vivo*, but the efficiency of rAAV-mediated transgene expression in the heart was both low (about 0.2%) and localized (See

applicants' specification page 2, lines 22 to 24). Thus prior to applicants' invention, the art did not describe a method for the stable and efficient transduction of cardiomyocytes using rAAV. WO 98/50079 ("Hammond"), cited by the Examiner in support of her rejection of claim 24 under 35 U.S.C. 102 and 103 for purported anticipation or obviousness, teaches transient expression of angiogenic transgenes in cardiomyocytes. Hammond does not consider transient expression to be a problem in their method and in fact Hammond teaches that transient expression is preferred in their method. As such, Hammond fails to provide the necessary teaching, suggestion or motivation for one of skill in the art to develop a method for stable and efficient transduction of cardiomyocytes using rAAV.

The Examiner in the Advisory Action states that stable and efficient expression does not require the virus to be integrated in the genome and thus transient expression of the encoded gene in the cell is considered stable and efficient transduction. However, Applicants have described the stable and efficient transduction of cardiomyocytes as significant numbers of cardiomyocytes transduced with AAV.

"For this invention, stable and efficient transduction means that significant numbers of cardiomyocytes are transduced and are capable of expressing the protein for a prolonged period of time. Stable and efficient transduction occurs over a period of time and can actually be observed over time as an increase in the percentage of transduced cardiomyocytes, as continued expression of the transgene, or as continued observation of the therapeutic effect at a molecular microscopic or macroscopic level." (page 8, lines 10-16)

Applicants have disclosed that their method transduces 10% of the cardiomyocytes in the heart, which increases over time, up to at least 8 weeks (see Figure 2), to levels of 25%, 40% and even 50%.

"By following the methods of the invention and by observing at particular times after transduction ranging over a few to many weeks, about 25%, about 40% or even about 50% of the cardiomyocytes will be transduced." (page 8, lines 22-24)

Such stable and efficient transduction of cardiomyocytes with rAAV is not taught or suggested in the prior art and one of skill in the art would not equate such transduction with "transient" transduction. And applicants have provided a detailed description of "a time

sufficient to stably and efficiently transduce cardiomyocytes perfused through said artery or sinus." See page 8, lines 27-30:

"The time of infusion contributes to achieving stable and efficient transduction of the cardiomyocytes as well. Thus the infusion time ranges from about 2 minutes to about 30 minutes, more preferably from about 5 minutes to about 20 minutes and most preferably is about fifteen minutes."

Because Hammond does not consider transient expression to be a problem, it is hindsight reconstruction to contend that applicant's claimed method is an obvious modification of Hammond's disclosure. Hammond does not teach or suggest delivering any rAAV for a sufficient time to achieve stable and efficient rAAV transduction, as recited in applicants' claims. Hammond merely provides general disclosures regarding the total amount of a virus to be delivered to a subject's heart. Kaplitt, cited in applicants' specification, teaches one of skill in the art to perfuse a heart with a rAAV vector and discloses that 0.2% of the cells displayed rAAV-mediated transgene expression. Kaplitt discloses injection of the circumflex coronary artery of pigs with a total of  $10^7$ - $10^8$  expressing units of AAV, which is within the range of  $10^6$ - $10^{14}$  particles that the Examiner contends is taught by Hammond. Thus, Kaplitt essentially used the method as taught by Hammond and did not achieve the results that are achieved by applicants' method. If one of skill in the art were to follow the teachings of Hammond, one would not design applicant's claimed method and would be surprised by the efficient and stable transduction that applicant achieves with the method as claimed.

"Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention." *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 32 USPQ2d 1017, 1019 (Fed.Cir. 1994). Hammond does not disclose infusing rAAV for sufficient time to achieve stable and efficient transduction of cardiomyocytes. Moreover, if one were to follow Hammond's method, which is essentially the method used by Kaplitt, one of skill in the art would not achieve applicants' results. Thus Hammond does not enable the stable and efficient transduction of cardiomyocytes with rAAV. For a reference to anticipate a claim, it must also enable the claim. *In re Sheppard* 145 USPQ 42, 45 (CCPA 1964) In view of the foregoing remarks it is clear that Hammond does not anticipate applicants' claims.

Regarding the rejection of the claims for purported obviousness:

"[A] proper analysis under \* 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . . Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."

*In re Vaeck*, 20 USPQ2d 1438, 1442 (CAFC 1991)

Hammond did not consider transient expression to be a problem in his system. Thus Hammond does not suggest and one of skill in the art would not be motivated by Hammond to administer rAAV for a sufficient time to achieve stable and efficient transduction of cardiomyocytes with rAAV. Hammond considered transient expression something to strive for:

As the experimental examples below demonstrated, transgene expression was maintained sufficiently long to allow collateral vessel development and concomitant restoration of normal heart function. Thus the angiogenic factor does not have to be present in the transfected cell for more than a few weeks to produce a therapeutic effect. (page 23, lines 1-4)

Moreover, one of skill in the art would have no reason to expect that significant numbers of cardiomyocytes from 10% to 25% to 40% and to 50% over time, could be transduced by using applicants' claimed method. Kaplitt *supra* teaches that only about 0.2% of the heart cells are transduced by injecting rAAV into porcine hearts and Hammond does not suggest stable and efficient transduction as a goal to achieve. Both the motivation to make a modification, and the expectation that in so making the modification the results would be successfully achieved, have to be found in the cited art and not in applicants' own disclosure:

In view of the foregoing it is clear that Hammond fails to render the claimed invention obvious.

The Examiner contends that claims 41, 42, 44, 46 and 47 are non-enabled. While

applicants respectfully disagree. Applicants have cancelled claims 41, 42, 44, 46 and 47 without prejudice, expressly reserving the right to pursue the subject matter of the cancelled claims in one or more subsequent applications. Thus, applicants have obviated the rejection under 35 U.S.C. 112, first paragraph.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. BSX 234 US1/10408799 from which the undersigned is authorized to draw.

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Respectfully submitted,

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